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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,316	08/22/2001	Ching-Leou Teng	ISIS-4824	1463

34138 7590 09/07/2005

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,316	TENG ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/01; 11/02; 8/03*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/22/2005 has been entered.

The amendment filed 6/22/2005 is acknowledged. The amendment has been entered. Claims 30-39 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/60012 (TENG et al. cited by Applicants in the IDS filed 8/18/2003) in view of U.S. Patent 5,672,359 (DIGENIS et al.) and further in view of MURANISHI (Critical Reviews in Therapeutic Drug Carrier Systems; 1990 Vol. 7, pages 1-33).

The instant claims are drawn to:

A method for enhancing the intestinal absorption of a drug in an animal, said method comprising administering to the animal:

(a) a first population of carrier particles comprising a drug-bioadhesive component; and,

(b) a second population of carrier particles comprising a penetration enhancer,

wherein intestinal tissue is activated by said penetration enhancer prior to the arrival of said drug and said first population and second population of carrier particles are administered in a single dosage (claim 30); wherein the first population is prepared as a tablet or a multiparticulate formulation (claim 31); wherein the second population is prepared as a tablet, multiparticulate, emulsion, microemulsion, or self-emulsifying system (claim 32); wherein the drug is an oligonucleotide (claim 33); wherein the penetration enhancer is a fatty acid (claim 34); wherein a bioadhesive of the drug-bioadhesive is a polyacrylic polymer (claim 35); and wherein the oligonucleotide is an antisense oligonucleotide (claim 36); wherein the bioadhesive comprises a polyacrylic

polymer (claim 38); wherein the bioadhesive further comprises a hydroxypropyl-methylcellulose (HPMC) (claim 39).

WO 99/60012 (TENG et al.) teaches a composition and method for enhancing the intestinal absorption of an oligonucleotide in an animal wherein the composition comprises a penetration enhancer such as a bile salt, fatty acid, or chelating agent (e.g., see page 3 lines 33-37) as well as other carriers or excipients including hydroxypropyl methylcellulose (HPMC) gelatin, polyacrylates, and starch (e.g., see page 18, lines 4-25; page 54, lines 22-35). WO 99/60012 teaches that the oligonucleotide can be ISIS-2302 which is 100% identical to SEQ ID NO: 1 (e.g., see page 24, lines 25-37 and page 37 lines 24-27). WO 99/60012 teaches a working example wherein an oral dosage comprising an oligonucleotide (ISIS-2302), a penetration enhancer(s) and an excipient is administered to an animal (e.g., see Example 15, pages 95-100). WO 99/60012 also teaches that the composition can be formulated into a tablet or capsule for oral administration wherein the tablet is constructed to provide for slow or controlled release of the active ingredients (e.g., see page 53, lines 1-23) and specifically indicates that the capsule for oral delivery may be a multicompartment hard capsule with controlled release properties as described in U.S. Patent 5,672,359 (DIGENIS et al.) (e.g., see page 55, lines 1-8).

WO 99/60012 does not explicitly teach that the drug (i.e., the oligonucleotide) is comprised in a first population of carrier particles with a bioadhesive and that the penetration enhancer is comprised in a second population of carrier particles wherein the first and second population are comprised in a single dosage form wherein the penetration enhancer activates the intestinal epithelium prior to arrival of the oligonucleotide/bioadhesive.

U.S. Patent 5,672,359 (DIGENIS et al.) teaches a capsule made from starch, gelatin or a hydrophilic polymer such as HPMC which by virtue of its design and composition provides an immediate and sustained mode of release of its pharmacologically active or otherwise desirable components (e.g., see column 1, lines 11-16). DIGENIS teaches that the capsule can comprise multiple compartments wherein the contents of the outer compartment(s) is released faster or before the release of the contents of the inner compartment(s) (e.g., see column 3, lines 26-52). DIGENIS teaches as a preferred embodiment that the capsule can be used for colonic delivery of drugs wherein absorption enhancers can be also be used to facilitate absorption of the drug. DIGENIS also teaches that the multicompartment capsule can be constructed to permit the release of the absorption enhancer prior to the release of the drug (see column 8, lines 25-38).

Furthermore, the use of penetration enhancers (also known as absorption enhancers) to facilitate the absorption of drugs into intestinal epithelium was well known in the art (e.g., see Muranishi). Specifically Muranishi teaches that many drugs are impermeable to outer tissue barriers and that delivery of the impermeable drugs through such barriers is one of the major interests in pharmaceutical research. Muranishi teaches that a number of absorption enhancers provide rapid absorption in the gastrointestinal tract or the skin (e.g., see abstract; page 27; etc.). Specifically, Muranishi reviews several absorption enhancers (including bile salts and fatty acids) which are capable of enhancing intestinal drug delivery by increasing the permeability of intestinal epithelium (e.g., see page 11-19). Therefore, one of skill in the art would have recognized that in order to increase the permeability of the intestinal epithelium, the absorption enhancer should reach the target tissue prior to the arrival of the drug.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use a formulation comprising the multicompartment capsule taught by DIGENIS such that the capsule comprised a penetration enhancer such as a bile salt, fatty acid, or chelating agent in the outer compartment(s) of the capsule wherein the capsule further comprises the oligonucleotide that is ISIS-2302 (SEQ ID NO: 1) and a bioadhesive agent(s), such as a polyacrylic polymer, HPMC and/or starch with a reasonable expectation of success.

The motivation to combine the references to create claimed invention is provided by WO 99/60012 (DENG et al.) who teaches a method of enhanced delivery of an oligonucleotide to intestinal tissue using a composition comprising a penetration enhancer, an oligonucleotide (SEQ ID NO: 1; ISIS-2302) and various excipients and specifically indicates that the multicompartment capsule taught by DIGENIS can be used as a controlled release capsule for delivering the oligonucleotide to the intestine of an animal.

Response to Arguments

Applicant's arguments, see page 4 of the communication filed 6/22/2005, with respect to the rejection(s) of claim(s) under 35 USC 102(b) and 35 USC 103(c) have been fully considered and, in light of the amendment, are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made under 35 USC 103 for the reasons indicated herein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art Unit 1635

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: The rejection of claims based on the '309 patent was discussed. Applicants indicated that they did not believe that the '309 patent taught a method wherein a first and second population of particles were separately comprised in a single dosage form. Applicants indicated that they believed the '309 patent teaches a formulation comprising all of the particles in a single dosage form, but not such that the two populations of particles were separately comprised within the single formulation. Applicants indicated they would consider amending the claims to better reflect that the two populations of particles were separately comprised in the single dosage form.